

REMARKS

I. Status of the Application

Claims 1, 2, 7-14, 18-25 and 37 are pending in the application. Claims 1, 2, 7-14 and 18-25 stand rejected under 35 U.S.C. §112, first paragraph. Claims 1, 2, 7-14, 18-25 and 37 stand rejected under 35 U.S.C. §112, second paragraph. Applicants gratefully acknowledge that the rejections of claims 1, 2, 7-9, 11-14 and 18-21 under 35 U.S.C. §103(a) as unpatentable over Levine et al., U.S. Patent No. 6,171,798, in view of Chang et al. (1998) *Oncogene* 16:1921, and of claim 10 under 35 U.S.C. §103(a) as unpatentable over Levine et al. in view of Chang et al., further in view of Ts'o et al., U.S. Patent No. 5,962,237, have been withdrawn.

Applicants have amended the claims to more clearly define and distinctly characterize Applicants' novel invention. Support for the amendments can be found in the specification and the claims as originally filed. Specifically, support for the amendments to claims 1, 2, 7 and 22 to recite "having a GenBank Accession Number of U67963" can be found in the specification at least at Figure 2A. Support for the amendments to these claims to recite "is encoded by" can be found in the specification at least at page 6, lines 16-19, where Applicants teach a nucleic acid sequence or molecule or corresponding peptide encoded by the nucleic acid sequence or molecule which demonstrates altered expression. The claims were further amended to correct formal matters. The amendments presented herein add no new matter.

Applicants respectfully request entry and consideration of the foregoing amendments, which are intended to place the case in condition for allowance.

II. Claims 1, 2, 7-14, 18-25 and 37 Are Enabled

At page 2, paragraph 4 of the instant Office Action, claims 1, 2, 7-14, 18-25 and 37 stand rejected under 35 U.S.C. §112, first paragraph, for lacking enablement. Applicants respectfully traverse this rejection.

The Examiner is of the opinion that the specification, while being enabling for methods of diagnosing oral cancer in a human subject that comprise detecting an altered level of expression of any of the nucleic acids/genes recited in independent claims 1, 2, 7 and 22 other than the molecule described as “lysophospholipase-like,” does not reasonably provide enablement for methods of monitoring expression levels in which any “lysophospholipase-like” molecule is detected. The Examiner states that unlike the other molecules encompassed by the claims, there is no particular, well-known gene or nucleic acid that corresponds to this designation, and that the claims themselves do not contain any further descriptive information. The Examiner concludes that while one of skill in the art could conduct further experimentation aimed at determining what particular “lysophospholipase-like” molecules are related to oral cancer, the outcome of such experimentation cannot be predicted, and thus it is unpredictable as to what type(s) of “lysophospholipase-like” genes/nucleic acids could actually be employed in the practice of Applicants’ invention.

Without acquiescing to this rejection, Applicants respectfully submit that claims 1, 2, 7 and 22 have been amended to recite lysophospholipase-like “having a GenBank Accession Number of U67963”. Applicants respectfully submit that GenBank is a well known database of nucleotide sequences. One of skill in the art need only enter the Accession Number in the GenBank database in order to obtain the nucleic acid sequence of the claimed gene (see

Attachment A). Thus, by providing a GenBank Accession Number, Applicants enable a person skilled in the art to make and use the claimed invention.

The Examiner is also of the opinion that the specification does not reasonably provide enablement for methods of “monitoring the progression” of oral cancer in a subject in which marker expression levels at different time points are detected in order to “monitor the progression of oral cancer.” The Examiner uses Ibrahim et al. to exemplify that no statistically significant correlation was found between tumor grade and expression levels of a group of oral cancer markers examined in oral cancer tissues taken from patients with different grades of tumors. The Examiner concludes that it would require undue experimentation to use Applicants’ invention in a manner reasonably commensurate with the instant claims. Applicants respectfully disagree.

Applicants respectfully submit that the instant specification provides ample direction and guidance to make and use the claimed invention. Applicants’ claimed invention is directed to a method for *monitoring the progression* of oral cancer in a human subject, the method comprising detecting in a first sample obtained from the human subject at a first point in time, a level of expression of a marker selected from a group of markers associated with oral cancer, detecting in a subsequent sample obtained from the human subject at a subsequent point in time, the level of expression of the marker, and *comparing the level of expression detected in the first and subsequent detecting samples* in order to *monitor the progression* of oral cancer, wherein the group of markers associated with oral cancer is encoded by a group of genes comprising p-53 responsive gene 2, beta A inhibin, human alpha-1 collagen type I gene, placental protein 11, BENE protein, neuromedin U, flavin containing monooxygenase 2, runt-related transcription factor 1, alpha 2 collagen type I, fibrillin 1, lysophospholipase-like having a GenBank Accession

Number of U67963, absent in melanoma 1, nonvoltage-gated 1 alpha sodium channel, protein tyrosine kinase 6 or epithelial membrane protein 1.

Monitoring progression can allow, for example, one of skill in the art to determine whether the cancer has spread to other parts of the oral cavity, or to ascertain whether all of the tumorous tissue has been removed by surgery, radiation and/or chemotherapy. Applicants' claimed method does *not* require that one of skill determine the *grade* of tumor based on the level of marker expression. Indeed, Applicants have determined that each of the claimed markers showed differential expression in well differentiated tumors, moderately differentiated tumors and poorly differentiated tumors.

The Examiner asserts that Applicants' specification provides no evidence that various levels of expression, e.g., correlate with tumor stage in any type of subject, as would be necessary in order for one to monitor tumor progression by detecting marker expression levels at various time points. Applicants disagree. Applicants have discovered that each of the claimed group of genes had differential marker expression in *five out of five* or *100%*, of paired cases of oral cancer (see page 22, lines 13-23 and Figure 2A). Thus, Applicants have determined that the claimed markers can be used to differentiate normal cells from tumor cells (see page 19, lines 19-22, page 22, lines 13-23, and Figure 2A). Accordingly, since these markers can be used to distinguish tumor cells from non-tumor cells, the claimed markers can serve to monitor oral cancer.

For at least these reasons, Applicants' specification enables a person of skill in the art to make and/or use the claimed invention. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1, 2, 7-14, 18-25 and 37 under 35 U.S.C. §112, first paragraph.

III. Claims 1-2, 7-14, 18-25 and 37 Are Definite

At page 5, paragraph 6 of the instant Office Action, claims 1-2, 7-14, 18-25 and 37 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection of the claims as amended herein.

The Examiner is of the opinion that claims 1, 2, 7-14, 18-25 and 37 are indefinite over the recitation of a gene/nucleic acid identified only as “lysophospholipase-like” in claims 1, 2, 7 and 22. The Examiner asserts that neither the specification nor the prior art provide a clear definition of this terminology that would allow one of skill in the art to identify the molecule or molecules that correspond(s) to this designation and, accordingly, it is not clear what molecule(s) is/are encompassed by the claims.

Applicants respectfully disagree. Applicants submit that the specification does describe “lysophospholipase-like” at least at Figure 2A, where Applicants provide the GenBank Accession Number for lysophospholipase-like. However, in order to expedite prosecution, Applicants have amended claims 1, 2, 7 and 22 to recite lysophospholipase-like “having a GenBank Accession Number of U67963.” Applicants respectfully submit that GenBank Accession Numbers are well-known and readily accessible to those of skill in the art. Claims 1, 2, 7 and 22 and claims depending therefrom are clear and definite because they reasonably convey to one skilled in the art what the invention is. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Examiner states that claim 1 is indefinite over the recitation of the phrase “wherein nucleic acids that hybridize differently correspond to genes of a gene expression profile that are

associated with oral cancer, and wherein the genes of a gene expression profile are selected from the group consisting of...epithelial membrane protein 1.” The Examiner is of the opinion that it is not clear what type of relationship or relationships between the “nucleic acids” of the claim and the “genes of a gene expression profile” is indicated or encompassed by the term “correspond.” The Examiner is also of the opinion that it is unclear from this language whether the determination of a single nucleic acid that hybridizes “differently” would be sufficient to meet the claim, and that while the claim recites a group of genes from which “genes of a gene expression profile” may be selected, the use of the plural terms “nucleic acids” and “genes” appears to indicate that multiple nucleic acids/genes of that group are necessary, and requests clarification.

Without acquiescing to the rejection, Applicants have amended claim 1 to replace the term “correspond to genes” with “encoded by a gene,” and to replace “nucleic acids” with “at least one nucleic acid” to clarify the language. Accordingly, Applicants request that this rejection be withdrawn.

The Examiner is of the opinion that claim 2 is indefinite over the recitation of the phrase “the nucleic acid corresponds to a gene selected from ...” as it is not clear what type of relationship or relationships between the “nucleic acid” of the claim and the “gene” of the claim is indicated or encompassed by the term “correspond,” and requests clarification.

Without acquiescing to the rejection, Applicants have amended claim 2 to replace the term “correspond” with “is encoded by” to clarify the language. Accordingly, Applicants request that this rejection be withdrawn.

The Examiner is of the opinion that claims 7-14, 18-25 and 37 are indefinite over the recitation of the phrase “the group of markers associated with oral cancer corresponds to a group

of genes comprising..." in claims 7 and 22 as it is not clear what type of relationship or relationships between the "group of markers" of the claims and the "group of genes" of the claims is indicated or encompassed by the term "corresponds," and requests clarification.

Without acquiescing to the rejection, Applicants have amended claims 7 and 22 to replace the term "correspond" with "is encoded by" to clarify the language. Accordingly, Applicants request that this rejection be withdrawn.

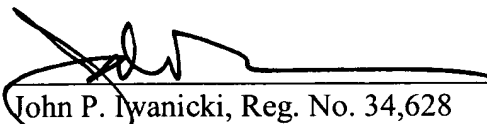
Applicants submit that the amended claims are definite and respectfully request that the rejection of claims 1-2, 7-14, 18-25 and 37 under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

IV. Conclusion

Having addressed all outstanding issues, Applicants respectfully request reconsideration and allowance of the case. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is requested to telephone the undersigned at the number below.

Respectfully submitted,

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John P. Iwanicki, Reg. No. 34,628
BANNER & WITCOFF, LTD.
28 State Street, 28th Floor
Boston, MA 02109
(617) 720-9600